REMARKS

This Amendment is responsive to the July 24, 2007 Office Action in which the rejection of claims 383, 384, 391, 393, and 394 under 35 U.S.C. §112, second paragraph was maintained, and extended to include claims 386 and 392; the rejection of claim 404 under 35 U.S.C. §112, first paragraph was maintained; the rejection of claims 382-405 under 35 U.S.C. §112, first paragraph was maintained and extended to include new claim 406; claims 382-402 were newly rejected under 35 U.S.C. §112, second paragraph; claims 382-406 were newly rejected under 35 U.S.C. §112, second paragraph; claim 382 was rejected under 35 U.S.C. §102(b) as being anticipated by Sutherland; claim 388 was provisionally rejected under 35 U.S.C. §101 as claiming the same invention as that of claim 159 of co-pending Application Serial No. 10/179,589 (double patenting); claim 388 was provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 159 of co-pending Application Serial No. 10/179,589; and claims 382-406 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 159, 163, and 170-173 of co-pending Application Serial No. 10/179,589. Applicant seeks favorable reconsideration of the above rejections in view of the amendments to the claims and remarks presented below.

Claims 382-402 and 406 have been canceled without prejudice to including and prosecuting such or similar claims in co-pending Application Serial No. 11/891,456, filed August 10, 2007. Accordingly, cancellation of such claims in the instant application does not constitute Applicant's agreement with or acquiescence to any of the rejections of any of these claims in the outstanding Office Action in the instant application.

Claims 383, 384, 386, and 391-394 were rejected under 35 U.S.C. §112, second paragraph. Inasmuch as claims 383, 384, 386, and 391-394 were cancelled, such rejection is moot and should be withdrawn by the Examiner.

Claims 382-402 were newly rejected under 35 U.S.C. §112, second paragraph, as being indefinite. Inasmuch as claims 382-402 were cancelled, such rejection is moot and should be withdrawn by the Examiner.

Claim 382 was newly rejected under 35 U.S.C. §102(b) as anticipated by Sutherland. Inasmuch as claim 382 was cancelled, such rejection is moot and should be withdrawn by the Examiner.

Claim 388 was newly provisionally rejected under 35 U.S.C. §101 for double patenting as allegedly claiming the same invention as that of claim 159 of co-pending Application Serial No. 10/179,589. Inasmuch as claim 388 was cancelled, such provisional rejection is moot and should be withdrawn by the Examiner.

Claim 388 was newly provisionally rejected on the nonstatutory ground of obvious-type double patenting as being patentably indistinct from that of claim 159 of co-pending Application Serial No. 10/179,589. Inasmuch as claim 388 was cancelled, such provisional rejection is moot and should be withdrawn by the Examiner.

OUTSTANDING REJECTIONS

Claims 382-406 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite. These claims were considered to be indefinite because it was not clear to the

Examiner whether bud formation is an intrinsic step of artery formation or whether the practitioner must perform further action to form an artery. Claims 382-402 and 406 have been cancelled by the instant Amendment. Applicant's remarks are thus directed to claims 403-405 and claims 407-412. Applicant disagrees that claims 403-405 and newly presented claims 407-412 fail to meet the definiteness requirements of 35 U.S.C. §112, second paragraph.

The Examiner questioned whether the formation of a bud would be an intrinsic step in artery formation or whether the practitioner would require further action. Examiner seems to be confusing the "definiteness" requirement of the second paragraph with the theory underlying Applicant's invention. The Examiner has not explained how an understanding of the underlying theory of the invention is required to render the claimed subject matter definite to one skilled in the medical art. Rather, it is clear from the specification that the only step required by the practitioner is that of injecting stem cells into a selected site in a patient's body. Once injected, the stem cells interact with the human host by differentiating along predetermined physiological developmental pathways to form a vascular bud which grows into an artery. One skilled in the art reading the claims in this light would clearly understand their scope.

Claim 404 was rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. Specifically, the Examiner states that the specification, as originally filed, does not provide antecedent support for "administration of cells to a damaged site in a leg of a patient." Applicant disagrees.

Example 18 provides a written description of intramuscular administration of cDNA clones to a damaged artery in the leg of a human patient to promote artery growth. The Examiner's statement that, "a damaged artery in a leg is not the same scope as damaged site in a

leg" is inept at best. The real issue is not whether the language "damaged site" is specifically recited in Example 18 but whether the concept of administrating a soft tissue promoter to a damaged site in the leg of a patient is conveyed by the original disclosure considered as a whole. See In re Anderson, 471 F. 2d 1237, 176 USPQ 331, (CCPA 1973) and In re Rasmussen, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981). The specification as filed is replete with disclosure relating to the concept of administering compositions to a "desired site" in the body for promoting the growth of soft tissue, such as an artery, as described in Example 18 and on page 53, lines 20-21 of the specification, which clearly teaches (page 53, lines 20-21) that, "the selection of sites can vary as desired."

Applicant further disagrees with the Examiner's statement that, "the specification does not envision administration of cells at the damaged artery." The written description requirement of the statute "serves to insure that the inventor had possession, as of the filing date of the application relied on, of the specific subject matter later claimed by him; how the specification accomplishes this is not material." In re Wertheim, 541 F.2d 257,262, 191 USPQ 90, 96 (CCPA 1976). The Court in In re Alton, 76 F.3d 1168, 37 USPQ 1578 (Fed. Cir. 1996) held that an applicant in satisfying the written description requirement:

> "...does not have to utilize any particular form of disclosure to describe the subject matter claimed, but 'the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.' In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (citation omitted). Put another way, 'the applicant must . . . convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention.' Vas-Cath, 935 F.2d at 1563-64, 19 USPQ2d at 1117. Finally, we have stated that '[p]recisely how close the original description must come to comply with the description

> requirement of section 112 must be determined on a case-by-case basis.' Eiselstein v. Frank, 52 F.3d 1035, 1039, 34 USPQ2d 1467, 1470 (Fed. Cir. 1995) (quoting Vas-Cath, 935 F.2d at 1561, 19 USPQ2d at 1116)."

It is trite law that the Examiner, when determining compliance with the description requirement of the statute, must consider the entire disclosure, see In re Anderson, supra. The Examiner has failed to explain where in claim 404 in calling for "injecting stem cells...at a damaged site" in a patient's leg defines subject matter completely outside the scope of the specification. The specification clearly contains a description of the claimed invention using descriptive words that fully set forth the claimed subject matter, albeit not *in haec verba.* See Eiselstein v. Frank, 52 F.3d 1035, 1038, 34 USPQ 2d 1467, 1470 (Fed. Cir. 1995).

Applicant submits that all the limitations of claim 404 appear in the specification as originally filed. The specification, starting at page 20 line 10, defines growth factors as compositions that promote soft and hard tissue growth. The specification is replete with description of inserting a soft tissue growth promoter at a desired (damaged) site in the body (pages 10, 18, 20, 21, 31, 32, 45, 52, 53, 56, and 62). Appropriate compositions which promote the growth of soft tissue within the scope of Applicant's invention are described as comprising a patient's own cells (pages 47 and 48) and particularly stem cells (pages 37, 40, 41, 42, 48, 51 etc.) including autologous and allogeneic global bone marrow stem cells (bone marrow mononuclear cells/BMCs) and adult stem cells collected from peripheral blood. One skilled in the art reading the subject application would understand that Applicant's invention is not limited to using a particular soft tissue promoter, such as the cDNA clones specifically described in Example 18 but, rather, includes the use of a broad class of described soft tissue promoters, including cells, such as stem cells. Claim 404 is directed to an alternative embodiment (elected

species) to the soft tissue promoter delineated in Example 18. One skilled in the art reading the subject matter disclosed on page 47, lines 22 through page 48, line 15 of the instant specification would readily understand that, as of the filing date, Applicant was in possession of the concept of employing a patient's own stem cells to promote the growth of an artery within the scope of claim 404.

Regarding the Examiner's statement that, "administration to arterial walls...[as described in Example 18] ...does not support the recitation of intramuscular injection," Applicant respectfully disagrees because those skilled in the medical arts to which the invention is directed fully understand that arteries are considered muscular vessels - possess a muscular component. Such fact can be confirmed by reference to any common medical dictionary.

The Examiner acknowledges that the instant specification teaches that cells are included in the class of soft tissue growth promoters described by Applicant. See, in particular, page 7, paragraph 14, of the July 24, 2007 Office communication where the Examiner states, "Therefore, *in the lexicon of this specification,* 'cells' may be a subgenus of 'growth factor'. " The respective Declarations of Drs. Heuser and Lorincz (submitted concurrently and of record) confirm that one skilled in the art to which the invention is directed would reach the same conclusion when reading the instant specification. The Examiner's reading and acknowledgement of the content of the specification is consistent with the mandate of the *en banc* CAFC decision in Phillips v. AWH Corporation, 415 F.3d 1303 (Fed. Cir. 2005).

Applicant believes that the Examiner's acknowledgement that cells are growth factors establishes as a material fact in this record that genes and cells are species of growth factors. In related application Serial No. 09/794,456, Examiner Kemmerer reached the same conclusion at

page 6, lines 1-8 in the February 22, 2006 Office communication. Perforce, this established material fact requires the Examiner to consider all relevant portions of Applicant's disclosure in evaluating the Section 112 "description" issue herein, including disclosures related to the genus "growth factor" and species, such as genes and cells. In view of this material fact, it was error for the Examiner to fail to consider the original disclosure as a whole, i.e., the above-mentioned genus and species relationship, when determining the specification's compliance or non-compliance with the description requirement of 35 U.S.C. §112, first paragraph. Thus, the Examiner's position disregards the tenants of relevant case law such as In re Anderson, supra; In re Rasmussen, supra; and Johnson and Farnham, 558 F.2d 1008, 194 USPQ 187, 195 (CCPA 1977).

In view of the Examiner's acknowledgement and relevant case law, Applicant is astonished by the Examiner's antithetical position at Page 17 of the outstanding Office Action that cells are so structurally and functionally distinct from cDNA clones, for example, "...that they must belong to distinct subgenera..." of soft tissue promoters and thus belong to distinct inventive entities. The Examiner has proffered no objective evidence that cells and cDNA clones function differently. Indeed, the record evinces that they possess a common functionality—they belong to a class of compositions that promote growth of soft tissues (arteries) in a human patient.

The Examiner is reminded that the facts (Law) of this case establish that the Patent and Trademark Office (hereinafter "PTO") is requiring an election of species in the instant application and in co-pending and related Application Serial Numbers 09/7794,456 and 09/836,750 has held cells (stem cells) to be a species within Applicant's class of growth

promoters (growth factors). The Examiner's reliance on case law relating to genus-species requirements misses the point. The present Examiner is bound by his and prior PTO holdings. It is unconscionable for the Examiner at this late stage of prosecution to contend otherwise.

Moreover, the PTO's species election requirement is consistent with the issuance of U.S. Patent No. 5,980,887 (hereinafter "Isner '887" and attached hereto as Exhibit A) and to U.S. Patent No. 5,328,470 to Nabel et al. (of record) and the treatment therein of cells and genes as a class. This is contrary to the Examiner's erroneous assertion of lack of functionality. It is further pointed out that the scope of claims issued by the PTO for Isner '887 encompass "VEGF cDNA" and "cells" as species of angiogenetic promoters, not different inventive entities. Isner '887 differs from the present invention by claiming injecting endothelial progenitor cells that are necessarily limited to promoting endothelial cell growth, not artery growth as required in the instant claims.

Further, the PTO's issuance of U.S. Patent No. 7,097,832, which bears a March 30, 2000 effective date, to Kornowski et al. (attached hereto as Exhibit B) in the same Class 424/93.7 as Isner '887 et al. evidences that the latter's use of endothelial progenitor cells does not achieve artery growth. This result is further confirmed in a post-filing date article published by the American Heart Association entitled, "Endothelial Progenitor Cells: More Than an Inflammatory Response" (attached hereto as Exhibit C). What the Examiner has failed to appreciate is that on this record Dr. Elia was the first to recognize that VEGF, cDNA, and stem cells are equivalent species within the genus soft tissue growth promoters for growing arteries in a human patient. This is a material fact established on this record regardless of Applicant's manner of "reduction of practice" for the present invention.

There can be no doubt that under current law the instant specification reasonably satisfies the description requirement of the statute by containing an equivalent description of the subject matter of claim 404, and the rejection should be withdrawn.

Claims 382-406 stand rejected under 35 U.S.C. §112, first paragraph, as failing to satisfy the enablement requirement. The Examiner has indicated that the prior rejection "is maintained and hereby extended to include new claim 406" but does not address the previous grounds with any degree of specificity. Rather, the Examiner perfunctorily concluded that Applicant's arguments filed on April 30, 2007 are non-persuasive. In any event, Applicant disagrees that the scope of protection provided by the pending claims is not adequately enabled by the application disclosure as originally filed under current law for the reasons set forth below.

Applicant notes the Examiner's determination in the Office Action dated August 31, 2007 that the specification is enabling for the scope of all claims in Applicant's co-pending Application Serial No. 10/179,589 except for claims 159, 166, 167, and 173. Inasmuch as the claims rejected herein are based upon the same specification that Applicant claims priority from and relies upon for enablement in said co-pending application and in view of the double patenting rejections made between the scope of claims from both applications, it would appear that a similar determination of enablement would be in order for the scope of subject matter set forth in the present claims.

Applicant believes that there are three important factors to consider when determining whether the instant specification contains a disclosure that would have enabled a skilled person in the medical art to make and use the claimed invention. When these factors are considered,

there can be no doubt that Applicant's specification provides an enabling disclosure. The three factors are discussed below.

First, there is a considerable body of disclosure provided by the subject application relating to Applicant's generic invention of promoting the growth of soft or hard tissue in human patients—including growing a new artery—by administering a broad class of growth factors including cellular growth factors such as stem cells suitable for affecting such tissue growth. In this regard, Applicant's specification (pages 20, 21, 30-32, and 38-42) provides a substantial body of disclosure regarding using a growth factor to form a bud and grow soft tissue in a human body. The specification (pages 10, 20, 21, 31, 32, and 37-52), describes a class of growth factors that broadly and specifically includes genes, nucleic acids, a patient's own cells (autologous cells), or universal cells, e.g., stem cells (global mononuclear bone marrow cells), etc., all of which are described to promote tissue growth through differentiation and morphogenesis. The Examiner has only considered the disclosure regarding enablement as it specifically relates to the elected growth factor species, cells. The Examiner's selective reading, which ignores Applicant's broad and specific disclosure relating to non-elected growth factor species disclosure, is clearly erroneous under current law. When an applicant elects to prosecute a species following an election requirement, the Examiner is not permitted to wear blinders and focus solely upon the elected species and ignore the scope of enablement provided by the specification as a whole, which includes the genus and non-elected species. There should be no doubt that the specification taken as a whole, when properly read and understood by one skilled in the art, meets the statutory requirement for enablement under current law.

Second, the Examiner has not taken issue, nor can issue be taken, with the fact that the administration techniques and administered compositions disclosed by Applicant were

individually old and well known as of the filing date of the instant patent application. The February 13, 2001 Declaration of Dr. G. Robert Meger (of record) demonstrates that the administration techniques and administered materials used in practicing the invention were known at the filing date of the application. The materials and administration techniques disclosed by Applicant were routinely employed in the medical art, but not in the claimed combination, at the time the instant application was filed. Applicant has also furnished, in this record, evidence that stem cells are harvested from bone marrow and blood of patients, as well as isolated at part of blood bank programs since the early 1950's.

Third, the prior Examiner has acknowledged that the level of skill in the medical art is high. Applicant agrees that the skill level is high when it is considered that many years of education, training, and experience are required in the medical field. The instant specification is addressed to and is understood by such highly skilled and trained persons.

Once the above-identified relevant materials and administration techniques set forth in the subject specification are properly considered in their entirety, Applicant believes that there should be no question that one skilled in the medical art is enabled to make and use the claimed invention. This conclusion is reinforced, as noted above, by the fact that the materials and administration techniques, but not the inventive results, were well known when the instant application was filed. MPEP Section 2164 states that the purpose of the enablement requirement is to describe the claimed invention in such terms to permit one skilled in the art to make and use the invention. Such Section cautions that detailed procedures for making and using the invention may not be necessary if the description of the invention itself is sufficient to permit those skilled in the art to make and use the invention. MPEP Section 2164.01 states that:

> A patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 929 F2d. 660, 661, 18 USPQ 2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F2d. 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986) cert denied, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist and Derrick Co.*, 730 F2d. 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984).

Applicant believes that the above caution is especially relevant to the instant factual situation where the Examiner has conceded that there was a high level of skill in the art at the time the instant application was filed and, coupled with the unchallenged evidence contained in Dr. Meger's Declaration, that all the materials, methods, and apparatus needed to practice the invention were well known at the time of the invention. Thus, Applicant submits that the instant disclosure clearly enables one skilled in the medical arts to make and/or use the full scope of the claimed invention without undue experimentation because a reasonable consideration of the three above-delineated factors and the interaction thereof leads to the inevitable conclusion that the disclosure is enabling to permit a skilled person in the medical art to make and use the claimed invention.

The Examiner has the burden to establish and support by convincing objective evidence a *prima facie* case of lack of enablement. For reasons set forth below, Applicant believes the Examiner has failed to meet such burden.

The first paragraph of the statue requires nothing more than objective enablement, and it is of no importance whether such teaching is set forth by use of illustrative examples or by broad terminology. As a general matter, an application's disclosure, which contains a teaching of how to make and use the invention in terms which correspond in scope to those used in describing the invention sought to be patented, is considered to be in compliance with the enabling requirement

of the statue. In re Marzocchi, 439 F.2d 220, 169 USPQ 367, 369-370 (CCPA, 1971). Further, "Section 112 does not require that a specification convince persons skilled in the art that the assertions therein are correct." [Emphasis added]. In re Robins, 429 F.2d 452, 166 USPQ 552 (CCPA, 1970).

When evaluating enablement, it is incumbent upon the Examiner to determine what subject matter each claim recites, i.e., the scope of protection sought for each claim. The scope of dependent claims are properly determined with respect to 35 U.S.C. §112, fourth paragraph. See MPEP Section 2164.08.

Initially, Applicant points out that it is evident the Examiner failed to consider the disclosure provided by the subject specification as a whole in determining compliance with the enablement requirement of the statute. The appropriate factual determination is whether the instant specification reasonably directs one skilled in the art how to make and use the claimed subject matter. As demonstrated above, the Examiner erroneously restricted the factual determination to the elected species of growth factor and, thusly, ignored those portions of the specification describing a broader generic invention and also ignored disclosure related to non-elected species. Applicant is entitled to have the entire disclosure considered in determining compliance with 35 U.S.C. §112, first paragraph. See In re Anderson, supra. and In re Johnson and Farnham, supra. Further, it is well settled that the test for enablement must take into consideration that which is known in the prior art – that a patent should preferably omit that which is well known/understood in the particular art to which the claims are directed. See MPEP Section 2164.01 and the authorities cited therein.

Turning to the specific reasons proffered by the Examiner in the outstanding Office Action regarding non-enablement, Applicant presents the following remarks.

In Paragraph 32 of the outstanding Office Action, the Examiner raises the issue of breadth of claim 382. Inasmuch as claim 382 was cancelled in the instant Amendment, no response appears to be required. However, Applicant notes that a large portion of this Paragraph is gratuitously concerned with non-elected inventions and thus lacks focus upon the claimed invention. The Examiner's remarks seem to require a standard not found in the patent statute—a requirement for an actual reduction to practice to support patentability. If this is the PTO position, then there should be a citation of applicable law or regulation that requires such a standard for patentability.

The Examiner in paragraphs 33 and 34 purports to support his position that the instant specification fails to teach that cells—stem cells such as global bone marrow stem cells—promote the growth of soft tissue organs, such as arteries. The Examiner attempts to limit Applicant's invention to the use of vascular epithelial growth factor gene (VEGF) described in Example 18. This is astonishing since the Examiner has been directed to the disclosure on pages 47 and 48 which describes forming organs or tissues using a patient's own cells. It is clear from page 48 that growth of an artery is contemplated. The art skilled is told that "reimplanting" a "patient's own stem cells results in differentiation and morphogenesis of a organ, i.e., artery, in a human patient." Perhaps, the Examiner fails to appreciate that "reimplanting" one's own stem cells requires that such stem cells must be recovered from one's own bone marrow or peripheral blood.

The Examiner in Paragraph 35 provides a lengthy dissertation addressing the failure of Example 18 to specifically teach the use of stem cells as a promoter of soft tissue growth, i.e., failure to teach (describe) using a stem cell to grow arteries. The Examiner incorrectly posits that "the question at hand is whether Example 18 provides guidance to one of skill in the art to use

cells in place of the VEGF cDNA in the example" to grow an artery in the leg of a patient. This question has already been answered by the Examiner and others in this record in the affirmative. See pages 10 and 11 of the instant Amendment.

Firstly, compliance with the first paragraph enablement requirement of Section 112 does not depend on the presence of an example, whether actual (working) or prophetic. Rather, the relevant issue is whether one skilled in the art having the entire specification disclosure, including the disclosures on pages 47 and 48 relating to reimplanting a patient's own (autologous) stem cells to cause differentiation and morphogenesis into an organ (artery) before such person, would expect that stem cell compositions could be injected into a patient's leg to grow an artery without undue experimentation. The Examiner has presented no cogent reasoning why one skilled in the art would not be enabled to inject stem cell compositions into a human patient and for good reason.

The claims in issue require stem cells, including those harvested from bone marrow and blood. The Examiner has failed to establish why one skilled in the art would not be able to extrapolate the disclosure and its examples across the entire scope of growth factors, including the use of cells, i.e., stem cells as the growth factor. See MPEP Section 2164.02. The Examiner's task is to consider the scope of enablement provided by the specification as a whole. Instead, highly relevant disclosure and examples regarding the genus growth factor and non-elected species were erroneously ignored.

Regarding the Examiner's taking issue with Applicant's extrapolation of dosages of DNA to cells on a per weight basis because gene therapy and cell therapy have different status in the art and, therefore, cannot be considered as functional equivalents of one another, one need look no further than the issuance of the Isner '887 patent to understand that PTO considers genes and

cells to be equivalent soft tissue growth promoters- species. Further, it is noted that Isner '887 is contemporaneous with the instant invention. Regarding the Examiner's statement that "[n]o such extrapolation is taught in the specification," Applicant points out that such extrapolations have been used for decades in the medical arts in regard to cell therapy. That which is well known in the art need not be included in Applicant's specification in order to comply with the enablement requirement of Section 112, first paragraph. See MPEP Section 2164.01. Applicant believes that the dosage extrapolation and the opinions in regard thereto expressed in the Declarations of Drs. Heuser and Lorincz speak for themselves. It is of particular note that the extrapolated dosages compare favorably (overlap) with the dosages of global bone marrow cells used by Strauer et al (2002 of record) for treating myocardial infarction in human patients, thereby confirming the reasonableness of the respective Declarants' opinions.

It is tempting to speculate that the Examiner's statement in paragraph 45 that Applicant's, "specification adds no new technical advance beyond that which is taught by Isner et al [Isner et al 4,296,100]" could be attributed to his reluctance to read the instant specification and "record" in its entirety or at least to a lack of understanding thereof because the art of medicine is not his specialty. It is interesting that Dr. Elia's improvement to the medical arts has fostered such prejudicial skepticism because of its manner of reduction to practice while the PTO issued the Isner '887 and Kornowski et al. '832 patent, which have a scope of claims including treating human patients using cell therapy based on "prophetic" disclosures but contained no human examples. In both instances, the respective patentees claimed to have achieved something no one else had done by simply writing it down. This did not preclude the PTO from issuing a patent. As noted in paragraph 46, "[i]t is a remarkable achievement to grow a new artery by implanting cells." In this regard, note the disclosure at pages 10 and 20 of the specification (which bears a

July 2, 1993 effective date) which describe employing tissue growth factors selected from a class of "active compositions" including organic matrices comprising allografts (page 10) for growing gum tissue, which is known to comprise blood vessels. Those skilled in the art to which the invention is directed understand that the term allograft refers to transplanted cells such as bone marrow stem cells. Based on this record, Dr. Elia was the first to recognize the role of bone marrow cells in achieving such a remarkable result.

One final point remains. The Examiner's statement that, "[f]or at least these reasons," i.e., the specifically enumerated reasons, the enablement rejection "must be maintained," which infers that other unspecified reasons are equally applicable. This statement is clearly in violation of the tenets of compact prosecution, especially in the present case where a prolonged prosecution before the PTO has seriously eroded Applicant's term should a patent be granted. It is the duty of the PTO to make all relevant rejections in order to preserve Applicant's due process rights.

The Examiner in paragraph 43 acknowledges that the term "bud" is understood to refer to "an organ primordium." By reading the instant specification, one skilled in the art would understand that the only active step for the "doer" or practitioner is placing stem cell compositions in the patient's body. The claims in issue are drawn to forming an artery. Once the stem cell composition is injected "at a selected site" the human body provides the nurturing necessary for the bud to grow along predetermined pathways to form an artery. The Examiner's statement that, "bud formation would not be a logical step in a situation where only a single layer of tissue is to be replaced" appears to be an acknowledgement that bud formation would be a logical step in growing an artery as claimed.

The Examiner in paragraphs 44, 45 and 46 authors a general patent-defeating theme that a prerequisite for obtaining a patent is that there must have been an actual reduction to practice. The Examiner cites no authority in regulations or law in support of this general theme and for good reason. In keeping with this theme, the Examiner concludes that Applicant's "prothetic" disclosure relevant to artery formation, "adds nothing new to that which was known and published three years before the instant application was filed by Isner et al. ["Circulation"]." Apparently, the Examiner fails to appreciate that the July 2, 1993 filing date of parent application Serial No. 08/087,185 (hereafter "the '185 application") subsequently granted as U.S. Patent No. 5,397,235, predates the Isner et al. Circulation publication by almost two years and teaches that active compositions/matrices such as, allografts (transplanted cells, such as bone marrow stem cells), promote the growth of gum (soft) tissue. Those skilled in the medical art understand that gum tissue necessarily comprises stratified epithelium densely packed with blood vessels. Further, it is noted that page 20 of the instant application, which is a progeny of continuing disclosure from the '185 application, describes many of the angiogenetic growth factors described in the Circulation publication. The Examiner's assertion that, "applicant adds no new technical advance beyond that which is taught by Isner et al. [Circulation]" evinces a total misunderstanding of Dr. Elia's contribution to the medical art. It is clear that the Isner et al. Circulation publication did not appreciate that stem cells promote the growth of arteries. Moreover, it is clear from Isner '887 that patentees failed to appreciate that global bone marrow stem cells promote the growth of arteries. The only support for the Examiner's statement that, "the instant specification does not even begin to work out the procedural differences between the protocol taught by Isner et al [Circulation publication], and any method that uses cells instead of cDNA" is the written statement itself. The truth is that no difference in procedural protocol exists

for administering stem cells using a hypodermic needle *vis-a-vis* genes, and this is readily apparent from reading the instant specification at page 21. The Examiner has failed to identify what protocol is missing from Applicant's specification that would prevent one skilled in the art from practicing the claimed subject matter. The Examiner's act of "writing it down," absent evidence or sound reasoning, is insufficient to overcome the objective enablement provided by the specification. cf In re Marzocchi, supra. Apparently, the Examiner fails to appreciate that the act of "writing down" a "prophetic" example which describes an embodiment based upon predicted results rather than work actually conducted is sufficient to satisfy a constructive reduction to practice. See MPEP 2164.02 and cited case law that stands for the proposition "the mere fact that something has not previously been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it." In re Chilowsky, 29 F. 2d 457, 461, 108 USPQ 321, 325 (CCPA 1956).

The "obviousness" issue raised in paragraphs 45 and 46 has merit only in the Examiner's mind because Applicant has never argued "that growth of an artery using stem cells was obvious in view of prior art in 1998." Applicant's specification teaches one skilled in the medical arts how to inject stem cell compositions with a hypodermic needle into a human patient to grow an artery. The Examiner should explain how the Court's decision in KSR v. Teleflex, 82 USPQ 2d 1385 (US 2007) dealing with "obviousness" (35 U.S.C. §103) pertains to the enablement rejection at hand. The Examiner acknowledges the novelty of the claimed method of implanting stem cells in a human patient to promote growth of an artery–a truly remarkable result—but considers it incredible for Applicant to purport to achieve such results without doing a single experiment. Applicant's discovery of an entirely new effect other than that of Isner '887 (growth

of arteries) produced by old agents (stem cells) using old means (hypodermic syringe) upon humans is novel, important, and patentable in the absence of prior art.

In summary, Applicant believes that the Examiner failed to provide sufficient objective evidence or reasoning to support a determination of lack of enablement under current law when considered *vis-à-vis* the evidence of enablement provided by Applicant's specification. Thus, the Examiner has failed to establish a *prima facie* case of lack of enablement, and this rejection should be withdrawn.

Assuming arguendo, that the Examiner somehow met the burden of establishing a *prima facie* case of lack of enablement, Applicant believes that any such case has been rebutted by the submission of the multiple Declarations of experts in the medical field—Drs. Wheeler, Finley, Meger, Lorincz, and Heuser (all of record). Please note that Fourth Supplemental Declarations of Dr. Heuser and Lorincz (attached hereto as Exhibits D and E, respectively) are being filed concurrently with the instant Amendment. The conclusions set forth in these multiple Declarations establish material facts relating to a determination of enablement regarding the presently pending claims. These highly skilled medical experts read and relied solely upon relevant portions of the specification, including generic, elected, and non-elected species portions, and reached independent determinations that one skilled in the medical art, armed with the knowledge presented in Applicant's disclosures, would be enabled to practice the claimed method and to predictably anticipate the results defined therein without need for resorting to undue experimentation.

The Examiner's failure to critically analyze and accord weight to Applicant's declaration evidence constitutes error as a matter of law. In re Alton, supra. It is trite law that the Examiner

must consider the probative value of such evidence *vis-à-vis* any asserted *prima facie* case. See In re Oetiker, at 1445, 24 USPQ 2d at 1444. In re Keller, 642 F.2d 413, 208 USPQ 871, (CCPA 1981). The Examiner, not being a skilled person in the medical art, must give weight to these expert opinions rather than reply upon his own opinion. See In re Neave, 370 F.2d 961, 152 USPQ 274, (CCPA 1967).

Applicant notes that the present Examiner has not repeated or specifically addressed the enablement rejection of the prior Examiner based upon the factors described In re Wands. Certainly, the Examiner did not specifically comment as to why the prior remarks of Applicant regarding these factors were not persuasive. Hence, it appears that the present Examiner does not rely upon such reasoning; and Applicant need not present remarks concerning these factors. As may be seen above, Applicant addressed the new positions stated and relied upon by the present Examiner in the outstanding Office Action regarding enablement, particularly whether such position is sufficient to establish a *prima facie* case of lack of enablement. In an abundance of caution and in an effort to not further burden the instant Amendment, Applicant hereby repeats and incorporates into the instant Amendment the remarks contained in the prior Amendments of April 30, 2007 and May 25, 2007 as rebuttal to the prior Examiner's remarks regarding the above-mentioned Wands factors.

For the above reasons, Applicant submits that the rejection for lack of enablement under 35 U.S.C. §112, second paragraph, is contrary to current law, and perforce, should be withdrawn.

Claims 382-406 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 159, 163, and 170-173 of co-pending Application Serial No. 10/179,589. Applicant notes such rejection and stands ready to submit an

appropriate Terminal Disclaimer upon an indication of allowable subject matter related to such claims.

From the foregoing remarks, Applicant submits that the instant application is in condition for allowance, and a Notice to such effect is respectfully requested. Should the Examiner have any questions or require additional information or discussion to place the application in condition for allowance, a phone call to the undersigned attorney would be appreciated.

Respectfully submitted,

Dated: 11/26/07

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